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**Title: Heterogeneity of striatal dopamine function in schizophrenia: meta-analysis of variance**

Short/running title: Dopaminergic heterogeneity in schizophrenia

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## **Abstract**

### **Background**

It has been hypothesized that dopamine function in schizophrenia exhibits heterogeneity in excess of that seen in the general population. However, this hypothesis has never been systematically tested.

### **Method**

We employed meta-analysis of variance to investigate inter-individual variability of striatal dopaminergic function in patients with schizophrenia and healthy controls. We included 65 studies reporting molecular imaging measures of dopamine synthesis or release capacities, D2/3 receptor (D2/3R) or transporter (DAT) availabilities, or synaptic dopamine levels, in 983 patients and 968 controls. Variability differences were quantified using variability ratio (VR) and coefficient of variation ratio.

### **Results**

Inter-individual variability of striatal D2/3R ( $VR=1.26$ ,  $p<.0001$ ) and DAT availabilities ( $VR=1.31$ ,  $p=.01$ ), and synaptic dopamine levels ( $VR=1.38$ ,  $p=.045$ ), but not dopamine synthesis ( $VR=1.12$ ,  $p=.13$ ) or release ( $VR=1.08$ ,  $p=.70$ ) capacities, were significantly greater in patients. Findings were robust to variability measure. Mean dopamine synthesis ( $g=0.65$ ,  $p=.004$ ) and release ( $g=0.66$ ,  $p=.03$ ) capacities, as well as synaptic levels ( $g=0.78$ ,  $p=.0006$ ) were greater in patients overall, but mean synthesis capacity did not differ relative to controls in treatment resistant patients ( $p>0.3$ ). Mean D2/3R ( $g=0.17$ ,  $p=.14$ ) and DAT ( $g=-0.20$ ,  $p=.28$ ) availabilities did not differ between groups.

### **Conclusions**

Our findings demonstrate significant heterogeneity of striatal dopamine function in schizophrenia. They suggest that while elevated dopamine synthesis and release capacities may be core features of the disorder, altered D2/3R

and DAT availabilities, and synaptic dopamine levels, may occur only in a subgroup of patients. This heterogeneity may contribute to variation in treatment response and side-effects.

## Introduction

Schizophrenia has long been linked to abnormalities in the dopamine system(1, 2). Molecular imaging techniques such as positron emission tomography (PET) and single photon (computed) tomography (SPE(C)T) have contributed to this understanding by allowing the investigation of the nature and loci of dopaminergic alterations in the living brain. A majority of studies have focused on the striatum, finding pronounced patient-control differences in (mean) dopamine synthesis and release capacity .(3) Mean differences in other aspects of dopaminergic function, such as D2/3 receptor (D2/3R) and dopamine transporter (DAT) availability, are small or non-significant.(3, 4) Thus, the dopaminergic abnormality in psychosis is now thought to primarily involve synthesis and release capacity.(2)

Several studies have explicitly investigated dopamine function in putative subtypes of schizophrenia. Three studies comparing treatment-responsive and non-responsive patients indicate that presynaptic dopaminergic alterations seen in the former group are not present in the latter.(5–7) Similarly, observations suggest that D2/3R availability predicts response to treatment(8), and is higher in patients with poor response or side-effects.(9, 10) Thus, heterogeneity in the dopamine system may delineate clinically meaningful subtypes of schizophrenia,(11, 12) linked to treatment response or side-effects.(5–7, 13)

However, while the number of such studies is relatively small, the past 30 years has seen a large number of patient-versus-control studies.(3) If there are indeed distinct dopaminergic subtypes,(11) we would expect to see this heterogeneity reflected in greater inter-individual variability in indices of dopaminergic function in patients relative to controls. In structural neuroimaging, several large recent studies have reported brain volumetric heterogeneity in patients with schizophrenia not seen in healthy controls (14–16). While individual studies have remarked on apparent variance differences in dopaminergic indices,(17–19) the question of dopaminergic heterogeneity – or indeed of other functional imaging measures – has not to our knowledge been systematically investigated. We therefore tested this hypothesis using *meta-analysis of variance*(14, 20, 21) to pool measures of

patient-control differences in inter-individual variability across the striatal dopaminergic molecular imaging literature. We additionally performed an updated meta-analysis of mean differences, including, for the first time, separate analyses of dopamine synthesis capacity, release capacity and synaptic dopamine levels.

## **Methods**

### **Study selection**

We searched MEDLINE, EMBASE and PsychINFO databases from inception to 31 December 2018, for studies reporting PET or SPECT measures of striatal dopaminergic function in patients with schizophrenia and controls. The following keywords were used: (Positron Emission Tomography OR PET OR Single photon emission tomography OR SPET OR Single Photon Emission Computed Tomography OR SPECT) AND (dopamine OR dopamine\*) AND (schizophrenia OR psychosis OR schizophren\*). We also searched references of previous meta-analyses(3, 22–24) to identify additional studies.

The inclusion criteria were: [1] original case-control studies reporting measures of striatal D2/3R or DAT availability, or dopamine synthesis or release capacity or synaptic dopamine levels, in patients and healthy controls; [2] studies of patients with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder; [3] sufficient data presented to calculate mean and standard deviation of measures for both groups; [4] Diagnosis in accordance with Diagnostic and Statistical Manual of Mental Disorders (version III-R, IV or V) or International Classification of Diseases (version 9 or 10) criteria; [5] study written in English; [6] for studies measuring D2/3R availability, patients not taking antipsychotic medication. Studies including patients with comorbid substance dependence were excluded.(25)

### **Data extraction & processing**

We extracted mean and standard deviations for patient and control groups. Data were extracted independently by two authors (SPB and IA); discrepancies were resolved by consensus. We also recorded details of duration of psychosis and of treatment, diagnoses and radioligand utilized. We combined results presented for multiple subgroups or sub-regions into a single measure for each study. In the latter case we assumed a correlation of 0.5 between sub-regions, although this may be conservative.(26) We extracted data presented in graphical form using the Web Plot Digitizer tool (<https://automeris.io/WebPlotDigitizer/>). Where the details required were not available

or not extractable these were requested. Where samples overlapped between studies, the study reporting the larger sample was included (see table S1 for further details).

## Outcome measures

The meta-analytic approach we use was first employed in ecology and evolutionary biology(21) and is described in further detail elsewhere.(20) Our first variability outcome measure is the log variability ratio (*lnVR*), the log-ratio of estimates of population standard deviations for patient and control groups,(21) as follows:

$$\ln VR = \ln \left( \frac{\hat{\sigma}_p}{\hat{\sigma}_c} \right) = \ln \left( \frac{s_p}{s_c} \right) + \frac{1}{2(n_p - 1)} - \frac{1}{2(n_c - 1)}$$

Where  $\hat{\sigma}_p$  and  $\hat{\sigma}_c$  are estimates of population standard deviations,  $s_p$  and  $s_c$  are reported sample standard deviations and  $n_p$  and  $n_c$  are sample sizes, for patient and control groups respectively in each case.

In biological systems, measures of dispersion frequently scale with mean, with higher means associated with greater variance.(27) It is therefore possible that variability differences seen using *lnVR* as an outcome measure, whilst real, may, in part, reflect differences in mean. We therefore also report results of analyses using log coefficient of variation ratio (*lnCVR*) as an outcome measure. This is the log-ratio of estimates of population coefficients of variation for patient and control groups, a measure which quantifies differences in variability after scaling to respective group means.(21) Log coefficient of variation ratio is given by:

$$\ln CVR = \ln \left( \frac{\hat{\sigma}_p / \bar{x}_p}{\hat{\sigma}_c / \bar{x}_c} \right) = \ln \left( \frac{s_p / \bar{x}_p}{s_c / \bar{x}_c} \right) + \frac{1}{2(n_p - 1)} - \frac{1}{2(n_c - 1)}$$

Where  $\bar{x}_p$  and  $\bar{x}_c$  are reported sample means for patient and control groups respectively. Details of sampling variance for *lnVR* and *lnCVR* may be found in Supplementary Methods.



We used Hedges'  $g$  as our effect-size measure for the meta-analysis of group differences in mean values.

### **Statistical analysis**

All analyses employed a univariate random-effects model. Summary effect sizes were calculated using restricted maximum-likelihood estimation. Where sufficient studies were found (at least 3), analyses were repeated for subgroups of treatment-naïve patients, treatment-responsive and treatment-resistant patients. To aid interpretation, summary effect sizes for  $\ln VR$  and  $\ln CVR$  were transformed back to a linear scale. Thus, a  $VR$  (or  $CVR$ ) of 1 indicates equal variability in patient and control groups, greater than 1 indicates greater variability in patients, and less than 1 indicates lower variability in patients.

### **Meta-regression**

We examined relationships between moderators of interest and outcome measures via mixed-effects meta-regression. Moderators included illness duration, proportion of treatment-naïve patients, proportion of patients with a diagnosis of schizophrenia (vs schizoaffective or schizophreniform disorders), year of publication, ligand utilized, and class of ligand. For D2/3R availability, ligand class included butyrophenones, benzamides, ergot derivatives and agonist tracers; for dopamine release studies class was restricted to benzamides vs agonist tracers. Ligands were of a single class for DAT availability and dopamine synthesis capacity. Given the large number of meta-regressions carried out, we adjusted for multiple comparisons using the Holm-Bonferroni method.(28)

### **Publication Bias and Inconsistency**

Inconsistency was assessed using the  $I^2$  statistic (by convention,  $I^2$  values of 0%, 25%, 50% and 75% are taken as indicative of no, low, moderate and high inconsistency respectively(29)). Publication bias was assessed by visual inspection of funnel plots, Egger's regression test for funnel plot asymmetry,(30) the trim-and-fill method(31) and the p-curve method.(32, 33) The p-curve approach was applied to each meta-analytic effect size for the data as a whole across molecular targets. Meta-analyses were conducted using the 'metafor' package(34) in the R statistical

programming language.(35) P-curve analyses were conducted using the online app (version 4.06; <http://www.p-curve.com/app4/>).

## **Results**

A total of 65 studies reporting data on 983 patients and 968 controls were included in the primary meta-analyses (see table 1; tables S1-2).

### **Dopamine D2/3 Receptor Availability**

Thirty-four studies reporting data on 485 patients and 485 controls were included in the primary analysis of D2/3R availability. Variability was significantly higher for all patients relative to controls for both VR and CVR (VR=1.26,  $p<0.0001$ ; CVR=1.22,  $p=0.007$ ; see figure 1, figure S2-S3). Mean D2/3R availability did not differ significantly between patients and controls (SMD=0.17,  $p=0.14$ ; see figure 2; figure S4).

### **Dopamine Release Capacity**

Six studies reporting data from 83 patients and 89 controls were included in the primary analysis of dopamine release capacity. Variability was not significantly different for all patients relative to controls for VR or CVR (VR=1.08,  $p=0.70$ ; CVR=1.31,  $p=0.27$ ; see figure 1, figure S4-S5). Mean dopamine release capacity was significantly higher in patients relative to controls (SMD=0.66,  $p=0.03$ ; see figure 2, figure S6).

### **Dopamine Synthesis Capacity**

Fifteen studies reporting data from 197 patients and 213 controls were included in the primary analysis of dopamine synthesis capacity. Variability did not differ significantly in patients relative to control groups for either measure (VR=1.12,  $p=0.13$ ; CVR=1.10,  $p=0.28$ ; see figure 1, figure S7-8). Mean dopamine synthesis capacity was significantly higher in patients relative to controls (SMD=0.65,  $p=0.004$ ; see figure 2, figure S9).

### **Synaptic Dopamine Levels**

Three studies reporting data from 40 patients and 46 controls were included in the primary analysis of synaptic dopamine levels. Variability was significantly higher for all patients relative to controls for both VR and CVR

(VR=1.38,  $p=0.045$ ; CVR=1.36,  $p=0.03$ ; see figure 1, figure S10-11). Mean synaptic dopamine levels were significantly greater in patients than in controls (SMD=0.78,  $p=0.0006$ ; see figure 2; figure S12).

### **Dopamine Transporter Availability**

Sixteen studies reporting data on 289 patients and 277 controls were included in the primary analysis of DAT availability. Variability was significantly higher in patients relative to controls for both measures (VR=1.31,  $p=0.01$ ; CVR=1.32,  $p=0.01$ ; see figure 1, figure S13-14). Mean DAT availability did not differ significantly between patients and controls (SMD=0.20,  $p=0.28$ ; see figure 2; figure S15).

### **Subgroup Analyses of Treatment Naïve Patients**

#### **Dopamine D2/3 Receptor Availability**

The subgroup analysis of treatment-naïve patients included 19 studies reporting data on 232 patients and 260 controls. Variability was higher in patient groups relative to controls for VR but not CVR (VR=1.20,  $p=0.04$ ; CVR=1.12,  $p=0.27$ ; figure S15-16). Mean D2/3R availability did not differ significantly between groups (SMD=0.25,  $p=0.19$ ; see figure S17).

#### **DAT Availability**

The subgroup analysis of treatment-naïve patients included 9 studies reporting data on 178 patients and 202 controls. Variability was higher in patients relative to controls for both VR and CVR (VR=1.45,  $p=0.02$ ; CVR=1.49,  $p=0.02$ ; figure S18-19). Mean DAT availability did not differ significantly between groups (SMD=-0.30,  $p=0.17$ ; see figure S20).

There were insufficient studies of treatment-naïve patients to perform subgroup analyses for synaptic dopamine, or dopamine synthesis or release capacity.

## **Subgroup analyses of resistant and treatment responsive/naïve patients**

### **Dopamine Synthesis Capacity**

Four studies reporting measures of dopamine synthesis capacity included patients described as treatment-resistant, or who were taking clozapine, which was taken to indicate resistance as it is generally restricted to such patients.(5, 7, 36, 37) Data for this subgroup were extractible separately for 3 studies comprising 37 patients and 38 controls. Neither measure of variability was elevated (VR=0.94, p=0.71; CVR=0.98, p=0.87; see figures S24-25), and mean dopamine synthesis capacity did not differ significantly between patients and controls (SMD=-0.40, p=0.34; see figure S26).

The subgroup of treatment-responsive/naive patients included 14 studies on 154 patients and 199 controls. Neither measure of variability was elevated (VR=1.13, p=0.12; CVR=1.11, p=0.33; see figures S21-22). A significant elevation in mean dopamine synthesis capacity was found ( $g=0.75$ ,  $p=0.0004$ ; see figure S23). Information on treatment resistance or clozapine use was not given in studies of other dopaminergic indices.

### **Meta-regression**

We found a significant effect of tracer on the standardized mean difference in dopamine release capacity ( $\chi^2=31.56$ ,  $p_{\text{adjusted}}=0.0001$ ). This effect was driven by the results of a single study(38) utilizing the D2/3R agonist radiotracer [11C]N-propyl-norapomorphine ([11C]NPA). No other effect survived adjustment for multiple comparisons (see table S4).

### **Publication Bias and Inconsistency**

Regression test indicated significant funnel plot asymmetry for dopamine synthesis capacity VR ( $z=2.02$ ,  $p=0.04$ ), but not for other variability measures. Asymmetry was also detected for dopamine synthesis capacity SMD

( $z=3.09$ ,  $p=0.002$ ) and DAT availability SMD ( $z=2.17$ ,  $p=0.03$ ) (see figures S25-S39). The trim and fill method suggested 5 missing studies for dopamine synthesis capacity VR, 5 missing studies for D2/3R availability CVR, 2 missing studies for dopamine release capacity SMD, and 2 missing studies for DAT availability SMD. P-curve analyses indicated the presence of evidential value for all measures. Inconsistency (between-study heterogeneity), ranged between low ( $I^2=0$ ; synaptic dopamine levels, all analyses) and high ( $I^2=79.33$ ,  $I^2=76.35$ ,  $I^2=76.23$ ,  $I^2=71.19$ ; DA release capacity CVR, D2/3R availability CVR, dopamine synthesis capacity SMD, DAT availability SMD). Further details of results of publication bias and inconsistency analyses may be found in table S5.

## Discussion

We found significantly greater inter-individual variability of striatal dopamine D2/3 receptor availability, dopamine transporter availability and synaptic dopamine levels in patients with schizophrenia compared to healthy controls. Variability of dopamine synthesis and release capacities did not differ between patients and controls. In contrast, standardized mean release capacity, and synaptic dopamine levels, were significantly greater in patients, while dopamine synthesis capacity was significantly greater in treatment responsive/naïve patients (and patients overall) but not in treatment resistant patients. Mean D2/3R and DAT availabilities did not differ between patients and controls. Variability findings were robust to choice of outcome measure, and are unlikely to be accounted for by methodological differences between studies, as all measures are calculated on a within-study basis. These results confirm findings of previous meta-analyses(3, 22) in a substantially enlarged sample, and, critically, extend them by demonstrating increased variability in D2/3R, DAT and synaptic dopamine levels, and elevation of mean synaptic dopamine levels.

Much recent work has focused on elucidating biological subtypes of schizophrenia. Several studies have reported differences between patient sub-groups, characterized by cognitive(39, 40) or symptomatic(5, 13, 37, 41–46) profile. Treatment responsiveness has emerged as a key dimension,(11, 47–49) with evidence for distinct abnormalities in resistant vs responsive psychoses.(50, 51) However, the question of whether patients exhibit greater inter-individual variability *per se* has remained unanswered. We previously reported evidence for greater variability in regional brain volumes in schizophrenia.(20) The present study extends this approach to neurochemical measures by systematically demonstrating greater inter-individual variability for a number of indices of striatal dopaminergic function.

These findings underscore the importance of evaluating group differences in variability alongside differences in mean. While we do not find significant mean differences for D2/3R or DAT availability, these measures are more variable in schizophrenia than in controls. This suggests that there may be a *subgroup* of patients in whom these measures *do* differ significantly, on average, from those of controls. While no qualitative rating of effect sizes for

variability differences(52) has yet been established, it is worth noting that those presented here for D2/3R and DAT availability, and synaptic dopamine levels, are larger than those for volumetric differences across all brain regions (ventricles excluded) reported previously.(20) These findings also suggest the need to routinely test for heteroscedasticity in case-control studies of patients with schizophrenia, and to use (potentially more efficient) statistical models where this is observed.

### **Limitations**

Funnel plot asymmetry was found for dopamine synthesis capacity VR (but not CVR), as well as for DA release capacity and DAT availability SMD. Publication bias is unlikely to account for asymmetry for VR, as the present work is, to our knowledge, the first in which a threshold for statistical significance has been applied to measures of variability in this literature, meaning that a selective publication incentive is unlikely to exist. We hope that the findings of the present work (and greater recognition of the importance of heterogeneity in schizophrenia and other disorders) encourage the publication of imaging and other results in which variability differences, currently perceived as unimportant, are present even in the absence of mean effects.

Moderate to high inconsistency was present in many analyses. Meta-regression suggests that this is unrelated to clinical variables, but may, in the case of dopamine release capacity SMD, relate to ligand characteristics. Several studies measuring dopamine synthesis capacity utilized non-quantitative analysis approaches, which may contribute to inconsistency. Only three studies measured synaptic dopamine levels, and this is reflected in relatively large summary effect size confidence intervals for this measure.

### **Interpretation**

There are several plausible interpretations of our findings. One is that apparent greater variability in D2/3R and DAT availability, and synaptic dopamine levels arises due to greater (or more variable) movement or other measurement artifact in patients. The differential extent of movement artifact has been associated with



differences in some MRI-based morphometric measurements,(53) and, while no effect has, to our knowledge, been reported for PET or SPECT imaging, it remains a possibility that we cannot definitively rule out. Likewise, we cannot definitively rule out the possibility that our findings are an artefactual effect of the greater structural variability seen in striatal regions in patients (20). However, if this were the case, we might expect to observe variability differences across all dopaminergic measures, which we do not.

Another possibility is that our findings reflect artificial homogeneity among controls, rather than heterogeneity in patients. Mental or physical comorbidities are frequent exclusion criteria for controls, potentially leading to recruitment of unusually healthy and homogeneous samples.(54) Furthermore, patients may be more likely to have subclinical medical or psychiatric comorbidities(55), recreational substance use, or medication exposure which may increase variability. However, meta-regression revealed no effects of confounding factors. While in this case we again might expect to observe variability differences for all indices, it is plausible that factors associated with illness selectively affect aspects of the dopamine system – most obviously prior antipsychotic treatment. Long-term blockade of D2 receptors may lead to upregulation in some subjects,(9, 10, 56) and thus increase inter-individual variability. However, variability effects were observed in treatment-naïve patients, and meta-regression found no evidence for a relationship between variability and prior treatment. Meta-regression also did not reveal a significant effect year of publication on outcome measures. We might expect incremental refinement of techniques over time, resulting in improved signal-to-noise ratio, to yield increased power to detect (true) mean effects, as well as (true) variability effects (as measured by CVR – VR would not be affected in this way as sampling variance depends only on sample size; see Supplementary Methods) over time. However, we cannot definitively rule this out, as meta-regression generally has low power to detect moderator effects.(57)

A further possibility is that our findings of greater inter-individual variability reflect greater *intra-individual* or *state* variability in patients. Schizophrenia is associated with state variability: for example circadian rhythm disruption and (58) affective instability(59), as well as symptomatic fluctuations over time. If these phenomena affect dopaminergic indices, then they could contribute to the greater inter-individual variability we report.

However, while indices of dopaminergic function have been reported to fluctuate on a circadian basis, (60) available evidence suggests that the magnitude of these fluctuations are if anything *lower* in patients with schizophrenia than in healthy controls.(61, 62) It has been argued that variation in mood state may relate to failure of dopaminergic homeostasis in the context of bipolar disorder (63), although, in the absence of longitudinal studies, this hypothesis remains somewhat speculative. Furthermore, while dopaminergic manipulations have been linked to sense of subjective well-being in both healthy and clinical samples, (64, 65) there remains no evidence linking dopamine homeostasis and mood variation outside of the context of a major mood disorder. In relation to symptomatic variation, cross-sectional studies suggest greater dopamine release capacity in acute relative to stabilized illness.(66) There is evidence that dopamine synthesis capacity increases in the transition from prodromal to frank psychosis,(67) although this does not appear to change following antipsychotic treatment and symptomatic improvement.(68) No other longitudinal studies examining state-related changes in dopaminergic indices have yet been published.

Finally, our variability findings may reflect heterogeneity in the nature of dopaminergic alterations in schizophrenia. Taken with our mean difference findings, one interpretation is that elevated dopamine synthesis and release capacity are core elements of the neurobiology of schizophrenia, seen in all patients, or at least in all treatment responsive patients (with large mean, but no variability differences), whilst abnormalities in D2/3R and DAT availabilities are seen only in a subgroup (with no overall mean, but large variability differences). Putatively increased D2/3R or reduced DAT levels could amplify the effect of dysregulated dopamine synthesis and release leading to psychosis in these patients. There is evidence from dual diagnosis patients that post-synaptic aspects of dopaminergic signal transduction augment effects of dopamine release to induce psychotic symptoms.(69) Alternatively, variability in D2/3R and DAT levels may reflect compensatory mechanisms in some patients. While these interpretations are speculative, they could be tested by examining multiple aspects of the dopamine system in the same patient. Synaptic dopamine levels show both large differences in mean and variability. It is possible – although speculative – that this dual effect is driven by greater mean dopamine release, modulated by

greater variability in reuptake by DAT. Alternatively, variability in DAT may modulate dopamine release directly, but be masked by the reverse transport effect of the amphetamine utilized in these studies.(70)

## **Implications**

A major implication of this work, in common with our previous study,(20) is that variability in the biology of schizophrenia is missed by solely examining group differences in mean. Previous studies have concluded that the primary abnormality of striatal dopamine function is one of synthesis and release, and that other aspects, such as D2/3R and DAT availability, do not differ from healthy controls.(3) The present work demonstrates that in a subset of patients these indices are also likely to fall substantially outside of the healthy range, and may be major components of pathophysiology in those patients. This heterogeneity, consistent with distinct dopaminergic subtypes of the disorder, has implications for precision medicine in schizophrenia, suggesting that a ‘one-size fits all’ approach to treatment may not succeed.

Our findings of greater variability in D2/3R availability could have therapeutic implications given that all first-line antipsychotic drugs act by blocking a substantial proportion of these receptors.(71) They suggest that variability in D2/3R availability could be an explanation for variability between patients in antipsychotic clinical response and susceptibility to extra-pyramidal and other D2/3R-mediated side-effects. Furthermore, they suggest that drug dosing based on studies in healthy volunteers may underestimate the width of therapeutic ranges, highlighting the need to include patients in phase I and II studies of novel drugs.

The finding of unaltered dopamine synthesis capacity variability is surprising, particularly given the link to treatment response,(5, 7, 37) which shows significant inter-individual variability.(72) Only four studies included patients with known treatment-resistance, or who were (or had previously been) taking clozapine(5, 7, 37, 73). Treatment resistant patients may be under-represented in other samples, perhaps due to difficulties recruiting or scanning these more symptomatic individuals. Alternatively, while dopamine synthesis capacity may be related to

treatment response at the individual level, the variability of this measure may, nevertheless, be similar to that seen in healthy controls. While there is a tension between the latter interpretation and the hypothesis of Howes and Kapur – that schizophrenia comprises at least two sub-groups, one characterized by elevated dopamine synthesis and release capacities and good treatment response; the other by unelevated capacities, and poor response (11) – our variability findings suggest that in addition, or instead, differences in D2/3R and/or DAT levels may contribute to incomplete or partial treatment response by increasing sensitivity to dopamine release in a subset of those patients with primarily dopaminergic abnormalities.. This would account for the large clinical variation in degree of response to and susceptibility to side-effects from treatment even within those patients who are classified as having responded. Further work is needed to test whether there are discrete dopaminergic sub-types and whether these are linked to treatment response and side-effects. Such sub-types should be manifest in the distribution of individual-patient data, for example as a bimodal distribution or, if one sub-group is substantially larger than the other, skewed data. It would be useful to test this in future individual-level patient data. Notwithstanding, our findings of large effect size elevations in mean striatal dopamine synthesis and release capacity and synaptic dopamine levels, coupled with evidence that show these are directly associated with symptom severity,(74, 75) identify these aspects of dopamine function as therapeutic targets.(76) However, it is important to note that our analyses are limited to striatum and that cortical dopamine release may be blunted.(77, 78)

## **Conclusions**

We demonstrate significantly greater inter-individual variability of dopamine receptor and transporter availabilities, and synaptic dopamine levels, coupled with large elevations in mean dopamine synthesis and release capacities, and synaptic dopamine levels, in patients with schizophrenia. These findings indicate that the pathophysiology of schizophrenia involves core alterations in dopamine synthesis and release capacity, and heterogeneity in other aspects of dopamine function.

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## Table & Figure Legends

Table 1: Summary of results of meta-analyses for all measures

Figure 1: Summary effect sizes for variability ratio (VR) and coefficient of variation ratio (CVR) of dopaminergic indices for all patients vs controls. Patients showed significantly greater variability of dopamine D2/3R availability (VR=1.26,  $p<0.0001$ ; CVR=1.22,  $p=0.007$ ), synaptic dopamine levels (VR=1.38,  $p=0.045$ ; CVR=1.36,  $p=0.03$ ) and dopamine transporter (DAT) availability (VR=1.29,  $p=0.01$ ; CVR=1.30,  $p=0.02$ ), but not of dopamine synthesis capacity (VR=1.12,  $p=0.13$ ; CVR=1.10,  $p=0.30$ ) or DA release capacity (VR=1.08,  $p=0.13$ ; CVR=1.31,  $p=0.27$ ), relative to controls. CI = Confidence Interval; VR = Variability Ratio; CVR = Coefficient of Variation Ratio.

Figure 2: Summary effect sizes for standardized mean differences of dopaminergic indices for all patients vs controls. Patients showed significantly greater mean dopamine release capacity (SMD=0.66,  $p=0.03$ ), dopamine synthesis capacity (SMD=0.65,  $p=0.004$ ) and synaptic dopamine levels (SMD=0.78,  $p=0.0006$ ) but not D2/3R availability (SMD=0.17,  $p=0.14$ ) or dopamine transporter (DAT) availability (SMD=-0.19,  $p=0.30$ ), relative to controls. CI = Confidence Interval; SMD = Standardized Mean Difference.

Figure 3: Diagram illustrating differences in mean and variability of dopaminergic indices in patients and controls. Blue elements are present in healthy controls and patients; orange elements represent differences in mean seen in patients. Differences in mean and variability illustrated on bell curves: blue = controls; orange = patients. Thus, reading from left to right, greater mean dopamine synthesis capacity is seen in (treatment responsive) patients, but the variability of this measure is not different. Greater variability of DAT availability is seen in patients, but mean is not significantly different. Greater dopamine release is seen in patients, but the

variability of this measure is not different. Greater mean and greater variability of synaptic dopamine levels are seen in patients. Finally, greater variability of D2/3R availability is seen in patients, but mean is not significantly different. Illustration created with BioRender (<https://biorender.com/>).



Table 1

				Variability Ratio			Coefficient of Variation Ratio			Standardized Mean Difference		
	Analysis	N studies	n patients, controls	Summary effect-size	95% CI	p-value	Summary effect-size	95% CI	p- value	Summary effect-size	95% CI	p- value
D2/3R Availability	All patients	34	485, 485	1.26	1.13, 1.41	<0.0001	1.22	1.06, 1.41	0.007	0.17	-0.07, 0.39	0.14
	Treatment Naïve	19	232, 260	1.2	1.01, 1.43	0.04	1.12	0.92, 1.35	0.19	0.25	-0.12, 0.63	0.19
DA Release Capacity	All patients	6	83, 89	1.08	0.72, 1.63	0.70	1.31	0.81, 2.10	0.27	0.66	0.06, 1.25	0.03
DA Synthesis Capacity	All patients	15	197, 213	1.12	0.97, 1.30	0.13	1.1	0.92 1.32	0.28	0.65	0.20, 1.10	0.004
	Treatment responsive/ naïve	14	154, 199	1.13	0.97, 1.33	0.12	1.11	0.91, 1.36	0.31	0.75	0.34, 1.17	0.0004
	Treatment- resistant	3	37, 38	0.94	0.67, 1.31	0.71	0.98	0.73, 1.31	0.87	-0.4	-1.22, 0.42	0.34
DAT Availability	All patients	15	289, 277	1.31	1.07, 1.60	0.01	1.32	1.06, 1.64	0.01	-0.2	-0.55, 0.16	0.28
	Treatment Naïve	9	178, 202	1.46	1.08, 1.97	0.01	1.5	1.08, 2.08	0.01	-0.29	-0.71, 0.13	0.17
Synaptic DA	All patients	3	40, 46	1.38	1.01, 1.89	0.046	1.36	1.03, 1.80	0.03	0.78	0.34, 1.23	0.0006